36) Figures 1, 17, 20, 24, 27, 29, 31, 33, 35, and 37 have been amended pursuant to MPEP 608.02(w) and are attached as replacement pages.

Respectfully submitted,

LYON & LYON LLP

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By: Samuel Tiu
Samuel N. Tiu
Reg. No. 47,997

LYON & LYON LLP
Suite 4700
633 W. Fifth Street
Los Angeles, CA 90071
Tel: (213) 489-1600
Fax: (213) 955-0440

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PATENT TRADEMARK OFFICE

MARKED-UP VERSION TO SHOW ALL CHANGES PURSUANT TO 37 CFR §1.21(b)(1)(iii)

IN THE SPECIFICATION

1) On page 11, line 5 of the specification, please delete the paragraph that begins with "Figure 1..." and ends with "...clustal W." and replace the deleted paragraph with the following replacement paragraph:

Figure 1 shows the seven homology sequences found to the query sequence: LVAFADFG-SVTFTNAEATSGGSTVGPSDATVMDIEQDGSVLTETSVSGDS-VTV (SEQ ID NO:1) by the program clustal W.

2) On page 12, line 16 of the specification, please delete the paragraph which begins with "Figure 17 represents..." and ends with "...to the invention." and replace the deleted paragraph with the following replacement paragraph:

Figure 17 represents the optimal sequence alignment between 8C001 (SEQ ID NO:10) and 1b4kA (SEQ ID NO:9) in PIR format as determined by the methods according to the invention.

3) On page 12, line 18 of the specification, please delete the paragraph which begins with "Figure 18 shows..." and ends with "...to the invention." and replace the deleted paragraph with the following replacement paragraph:

Figure 18 shows the crystal structure of law5 on the left and the structure of SC001 (SEQ ID NO:10) on the right as predicted by the methods according to the invention.

4) On page 12, line 20 of the specification, please delete the paragraph which begins with "Figure 19 shows. ..." and ends with "...with oleic acid." and replace the deleted paragraph with the following replacement paragraph:

Figure 19 shows a space filling representation of chain A from 1dkf (SEQ ID NO:12) co-crystalized with oleic acid.

5) On page 12, line 22 of the specification, please delete the paragraph which begins with "Figure 20 ..." and ends with "...of the invention." and replace the deleted paragraph with the following replacement paragraph:

Figure 20 shows the PIR alignment of 1dkf (denoted as gi7766906) (SEQ ID NO:12) and the sequence of chain A of structure 1a28 (SEQ ID NO:11) according to the methods of the invention.

6) On page 13, line 1 of the specification, please delete the paragraph which begins with "Figure 21 ..." and ends with "...of 1dkf." and replace the deleted paragraph with the following replacement paragraph:

Figure 21 shows a rainbow ribbon overlay between the predicted structure and the crystal structure of chain A of 1dkf (SEQ ID NO:12).

7) On page 13, line 3 of the specification, please delete the paragraph which begins with "Figure 22 ..." and ends with "...binding pocket." and replace the deleted paragraph with the following replacement paragraph:

Figure 22 shows an overlay of the predicted structure according to the methods of the invention 1dkf (SEQ ID NO:12) and the crystal structure for 22 key residues that form the oleic acid binding pocket.

8) On page 13, line 8 of the specification, please delete the paragraph which begins with "Figure 24 ..." and ends with "...denoted la28A." and replace the deleted paragraph with the following replacement paragraph:

Figure 24 shows the alignment according to the methods of the invention in PIR format between the sequence of the estrogen receptor (denoted as gi3659931) (SEQ ID NO:14) and the sequence of chain A of structure 1a28, denoted 1a28A (SEQ ID NO:13).

9) On page 13, line 17 of the specification, please delete the paragraph which begins with "Figure 27 ..." and ends with "...to the invention." and replace the deleted paragraph with the following replacement paragraph:

Figure 27 shows the alignment formed from the methods of the invention in PIR format between the sequence of halorhodopsin, denoted 1e12A (SEQ ID NO:16), and the sequence of bacteriorhodopsin, denoted 1c3wA (SEQ ID NO:15) made by the methods according to the invention.

10) On page 13, line 20 of the specification, please delete the paragraph which begins with "Figure 28..." and ends with "...code 1e12." and replace the deleted paragraph with the following replacement paragraph:

Figure 28 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in figure 27, compared to the halorhodopsin crystal structure, chain A of PDB code 1e12 (SEQ ID NO 16).

11) On page 14, line 1 of the specification, please delete the paragraph which begins with "Figure 29..." and ends with "...1f88A." and replace the deleted paragraph with the following replacement paragraph:

Figure 29 shows the alignment, formed from the methods according to the invention, in PIR format, between the sequence of bacteriorhodopsin, denoted 1c3wA (SEQ ID NO:18), and the sequence of rhodposin, chain A of PDB structure 1f88, denoted 1f88A (SEQ ID NO:17).

12) On page 14, line 4 of the specification, please delete the paragraph which begins with "Figure 30..." and ends with "...code 13cw." and replace the deleted paragraph with the following replacement paragraph:

Figure 30 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in Figure 29, compared to the bacteriorhodopsin crystal structure, chain A of PDB code 1c3w (SEQ ID NO:18).

13) On page 14, line 7 of the specification, please delete the paragraph which begins with "Figure 31..." and ends with "...denoted 6prcL." and replace the deleted paragraph with the following replacement paragraph:

Figure 31 shows the alignment, formed from the methods according to the invention, in PIR format, between the sequence of a membrane spanning chain of the photosynthetic reaction center, denoted 6prcM (SEQ ID NO:20), and the sequence of a different chain from the photosynthetic reaction center, chain L of PDB structure 6prc, denoted 6prcL (SEQ ID NO:19).

14) On page 14, line 11 of the specification, please delete the paragraph which begins with "Figure 32 ..." and ends with "...code 6prc." and replace the deleted paragraph with the following replacement paragraph:

Figure 32 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in Figure 31, compared to the crystal structure for chain M of PDB code 6prc (SEQ ID NO:20).

15) On page 14, line 14 of the specification, please delete the paragraph which begins with "Figure 33 ..." and ends with "...denoted 1qj8A." and replace the deleted paragraph with the following replacement paragraph:

Figure 33 shows the alignment according to the invention in PIR format between the sequence of ompA, denoted 1bxwA (SEQ ID NO:22), and the sequence of ompX, chain A of PDB structure 1qj8, denoted 1qj8A (SEQ ID NO:21).

16) On page 14, line 17 of the specification, please delete the paragraph which begins with "Figure 34 ..." and ends with "...code 1bxw." and replace the deleted paragraph with the following replacement paragraph:

Figure 34 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in figure 33, compared to the ompA crystal structure, chain A of PDB code 1bxw (SEQ ID NO:22).

17) Starting on page 14, line 20 of the specification, please delete the paragraph which begins with "Figure 35 ..." and ends with "...protein 2por." and replace the deleted paragraph with the following replacement paragraph:

Figure 35 shows the alignment according to the invention in PIR format between the sequence of ompK36, denoted 1osmA (SEQ ID NO:24), and the sequence of porin protein 2por (SEQ ID NO:23).

18) On page 15, line 1 of the specification, please delete the paragraph which begins with "Figure 36 ..." and ends with "...code 1osm." and replace the deleted paragraph with the following replacement paragraph:

Figure 36 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in figure 35, compared to the ompK36 crystal structure, chain A of PDB code 1osm (SEQ ID NO:24).

19) On page 15, line 4 of the specification, please delete the paragraph which begins with "Figure 37 . . ." and ends with "...denoted 2mprA." and replace the deleted paragraph with the following replacement paragraph:

Figure 37 shows the alignment, formed from the methods according to the invention, in PIR format, between the sequence of sucrose-specific porin, denoted

1a0tP (SEQ ID NO:26), and the sequence of maltoporin, chain A of PDB structure 2mpr, denoted 2mprA (SEQ ID NO:25).

20) Starting on page 15, line 7 of the specification, please delete the paragraph which begins with "Figure 38..." and ends with "...1a0tP." and replace the deleted paragraph with the following replacement paragraph:

Figure 38 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in figure 37, compared to the sucrose-specific porin crystal structure, chain P of PDB code 1a0tP (SEQ ID NO:26).

21) On page 16, line 9 of the specification, please delete the paragraph which begins with "Table 7..." and ends with "...by gapped-BLAST." and replace the deleted paragraph with the following replacement paragraph:

Table 7 provides PDB structures found to have sequence similarity to SC001 (SEQ ID NO:10) by gapped-BLAST.

22) Please delete the paragraph starting on page 21, line 3 of the specification with "Another preferred . . .", and ending on page 22, line 10 of the application with ". . . SVTV." and replace the deleted paragraph with the following replacement paragraph:

Another preferred method for determining BRIDGE/BULGE information employs an algorithm such as BLAST, S. F. Altschul, W. Gish, W. Miller, E. W. Meyers, and D. J. Lippman, *J. Mol. Biol.* 215, 403-410 (1990), to determine a set of homology sequences to the query sequence and the template sequences from any large sequence database that contains a statistically representative cross section of many sequences across multiple genomes. Preferably the databases that are used to determine the BRIDGE/BULGE lists according to this preferred embodiment include all the known sequences with homologies of at least 45% to the query and template sequences. A suitable database would be the non-redundant protein sequence databank at the NIH, which currently contains more than 600,000 sequences from more than 100 different organisms. A BRIDGE/BULGE list may then be determined from the sequence homology sets formed from query sequence and the template sequences using any multiple sequence alignment algorithm known in the art, such as clustalW, J. D. Thompson, D. G. Higgins, T. J. Gibson, *Nucl. Acids Res.* 22, 4673-4680 (1994). Figure 1 shows the 7 homology sequences found (performed by clustalW) for the sequence:

LVAFADFGSVTFTNAEATSGGSTVGPSDATVMDIEQDGSVLTETSVSGDSVTV (SEQ ID NO:1).

23) On page 22, line 12 of the specification please delete the paragraph which begins with "With respect . . .", and ending with ". . . dimensional structures." and replace the deleted paragraph with the following replacement paragraph:

With respect to the query sequence (SEQ ID NO:1), the multiple sequence alignment contains 2 different one-residue bulge regions, represented by the "G-S" and "S-V" points in the query sequence (SEQ ID NO:1). The multiple alignment in Figure 1 also contains one bridge region, where the residues "STVGPSD" in the query sequence (SEQ ID NO:1) are bridged by a gap region in sequence 4 (SEQ ID NO:5). Note that if three-dimensional models of the homology sequences exist it is possible to verify that each of the bridges and bulges found comply with the physical limitations imposed by the three dimensional structures.

24) Please delete the paragraph starting on page 40, line 18 with "Example 6 demonstrates..." and ending on page 41, line 2 with "...in Table 7." and replace the deleted paragraph with the following replacement paragraph:

Example 6 demonstrates that the methods of the invention, in combination with widely available homology modeling packages, may be used to predict accurate three dimensional structures at low sequence homologies . In this example consider the three dimensional structure of SC001 (orf YGL040C) (SEQ ID NO:10) from Brewer's yeast (*Saccharomyces cerevisiae*) is determined based upon a low homology template sequence. In order to build a BRIDGE/BULGE list, gapped-BLAST was used to determine a list of protein structures in the Protein Databank with similar sequences to the query sequence, SCOO1 (SEQ ID NO:10). The 8 PDB similar structures that were found are shown in Table 7.

25) On page 41, line 7 of the specification, please delete the paragraph which begins with "In order to. ..." and ends with "...Table 8." and replace the deleted paragraph with the following replacement paragraph:

In order to further demonstrate the ability of the preferred alignment methods to generate accurate structures at low sequence homologies, the sequence 1b4kA (SEQ ID NO:9) (shown in Table 7) was used as a template sequence and to generate the BRIDGE/BULGE list. The structure alignment between SCOO1 (SEQ ID NO:10) and 1b4kA (SEQ ID NO:9) has a 35% sequence homology and a reliable structural model for sequence SC001 (SEQ ID NO:10) built from 1b4kA (SEQ ID NO:9) is not present in MODBASE. Structure 1b4kA (SEQ ID NO:9) is 326 residues long; there are 211 structurally aligned proteins in the FSSP file for 1b4kA (SEQ ID NO:9). These alignments yield 3444 possible bridges and bulges for this structure, some of which are shown below in Table 8.

26) On page 42, line 4 of the specification, please delete the paragraph which begins with "The optimal sequence ..." and ends with "...of known structures." and replace the deleted paragraph with the following replacement paragraph:

The optimal sequence alignment between SC001 (SEQ ID NO:10) to 1b4kA (SEQ ID NO:9) according to the methods of the invention is shown in PIR format in Figure 17. The gap penalties used for this alignment were gap opening

and extension penalties of 10.0 and 1.5, respectively, with bridge and bulge opening and extension penalties of 1.0 and 0.3, respectively. These gaps penalties were determined by optimizing the alignment obtained for sets of known structures.

27) On page 43, line 1 of the specification, please delete the paragraph which begins with "The PIR format ..." and ends with "...methods failed." and replace the deleted paragraph with the following replacement paragraph:

The PIR format alignment was then used as the alignment input for the MODELLER homology modeling software. The structure built by MODELLER using this alignment is compared to the actual crystal structure of SC001 (SEQ ID NO:10), 1aw5, in Figure 18 (1aw5 is on the left, prediction on the right). The alpha-carbon CRMS is 2.11Å for 326 matched residues demonstrating that once again, the preferred alignment methods when used in combination with a homology modeling program were able to generate an accurate structural model when current methods failed.

28) Please delete the paragraph starting on page 43, line 13 with "Consider the three ..." and ending on page 44, line 2 with "...overlay to 2.2Å." and replace the deleted paragraph with the following replacement paragraph:

Consider the three dimensional structure of RXR retinoic acid receptor, chain A of PDB code 1dkf (SEQ ID NO:12). For this structure, the protein was co-crystallized with oleic acid. A ribbon diagram of the structure, showing the oleic acid ligand in space filling representation is shown in Figure 19. Figure 20 shows the STRUCTFAST alignment in PIR format between the sequence of 1dkf (denoted as gi7766906) (SEQ ID NO:12) and the sequence of chain A of structure 1a28, denoted 1a28A (SEQ ID NO:11). In total, 197 residues are aligned to the template, and sequence identity is only 19%. Figure 21 shows a rainbow ribbon overlay between the predicted structure and the crystal structure of chain A of 1dkf) (SEQ ID NO:12). The alpha-carbon CRMS for the best aligning 158 residues (80% of the complete 197 residues) is 1.6 Å. Figure 22 shows an overlay of the predicted structure (darker) and crystal structure (lighter) for the 22 key residues that form the oleic acid binding pocket. The backbone atoms in these 22 residues overlay to 1.7Å, and all of the heavy atoms in the residues, including the sidechain atoms, overlay to 2.2Å.

29) On page 44, line 3 of the specification, please delete the paragraph which begins with "Consider the three ..." and ends with "...overlay to 1.8Å." and replace the deleted paragraph with the following replacement paragraph:

Consider the three dimensional structure of an estrogen receptor, chain A of PDB code 1a52 (SEQ ID NO:14). For this structure, the protein was co-crystallized as a dimer with estradiol. A stick diagram of the structure, showing

the estradiol ligands in space filling representation is shown in Figure 23. Figure 24 shows the alignment according to the methods of the invention, in PIR format, between the sequence of the estrogen receptor (denoted as gi3659931) (SEQ ID NO:14) and the sequence of chain A of structure 1a28, denoted 1a28A (SEQ ID NO:13). In total, 241 residues are aligned to the template, and sequence identity is 23%. Figure 25 shows a rainbow ribbon overlay between the predicted structure according to the methods of the invention of the estrogen receptor and the crystal structure of chain A of 1a52 (SEQ ID NO:14). The alpha-carbon CRMS for the best aligning 193 residues (80% of the complete 241 residues) is 1.9 Å. Figure 26 shows an overlay of the predicted structure (darker) and crystal structure (lighter) for the 19 key residues that form the estradiol binding pocket. The backbone atoms in these 19 residues overlay to 0.8Å, and all of the heavy atoms in the residues, including the side-chain atoms, overlay to 1.8Å.

30) On page 45, line 1 of the specification, please delete the paragraph which begins with "Figure 27 ..." and ends with "...is 0.91 Å." and replace the deleted paragraph with the following replacement paragraph:

Figure 27 shows the alignment, in PIR format, between the sequence of halorhodopsin, denoted 1e12A (SEQ ID NO:16), and the sequence of bacteriorhodopsin, denoted 1c3wA (SEQ ID NO:15) made by the methods according to the invention. In total, 233 residues are aligned to the template, and the sequence identity is 32%. Figure 28 shows a rainbow ribbon overlay between

the three-dimensional structure created using the alignment in figure 27, compared to the halorhodopsin crystal structure, chain A of PDB code 1e12 (SEQ ID NO:16). The alpha-carbon CRMS for the best aligning 187 residues (80% of the complete 233 residues) is 0.91 Å.

31) On page 45, line 9 of the specification, please delete the paragraph which begins with "Figure 29..." and ends with "...5,24 Å." and replace the deleted paragraph with the following replacement paragraph:

Figure 29 shows the alignment formed from the methods according to the invention in PIR format, between the sequence of bacteriorhodopsin, denoted 1c3wA (SEQ ID NO:18), and the sequence of rhodposin, chain A of PDB structure 1f88, denoted 1f88A (SEQ ID NO:17). In total, 214 residues are aligned to the template, and the sequence identity is only 13%. Figure 30 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in figure 29, compared to the bacteriorhodopsin crystal structure, chain A of PDB code 1c3w (SEQ ID NO:18). The alpha-carbon CRMS for the best aligning 172 residues (80% of the complete 214 residues) is 5.24 Å.

32) Please delete the paragraph starting on page 45, line 17 with "Figure 31 shows ..." and ending on page 46, line 2 with "...is 1.00 Å." and replace the deleted paragraph with the following replacement paragraph:

Figure 31 shows the alignment, formed from the method according to the invention, in PIR format, between the sequence of a membrane spanning chain of the photosynthetic reaction center, denoted 6prcM (SEQ ID NO:20), and the sequence of a different chain from the photosynthetic reaction center, chain L of PDB structure 6prc, denoted 6prcL (SEQ ID NO:19). In total, 259 residues are aligned to the template, and the sequence identity is 28%. Figure 32 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in Figure 31, compared to the crystal structure for chain M of PDB code 6prc (SEQ ID NO:20). The alpha-carbon CRMS for the best aligning 207 residues (80% of the complete 259 residues) is 1.00 Å.

33) On page 46, line 3 of the specification, please delete the paragraph which begins with "Figure 33..." and ends with "...is 2.59 Å." and replace the deleted paragraph with the following replacement paragraph:

Figure 33 shows the alignment, according to the methods of the invention, in PIR format, between the sequence of ompA, denoted 1bxwA (SEQ ID No:22), and the sequence of ompX, chain A of PDB structure 1qj8, denoted 1qj8A (SEQ ID NO:21). In total, 153 residues are aligned to the template, and the sequence identity is only 21%. Figure 34 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in figure 33, compared to the ompA crystal structure, chain A of PDB code 1bxw (SEQ ID No:22). The

alpha-carbon CRMS for the best aligning 172 residues (80% of the complete 214 residues) is 2.59 Å.

34) On page 46, line 10 of the specification, please delete the paragraph which begins with "Figure 35..." and ends with "...is 3.11 Å." and replace the deleted paragraph with the following replacement paragraph:

Figure 35 shows the alignment, according to the methods of the invention, in PIR format, between the sequence of ompK36, denoted 1osmA (SEQ ID NO:24), and the sequence of porin protein 2por (SEQ ID NO:23). In total, 323 residues are aligned to the template, and the sequence identity is only 12%. Figure 36 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in figure 35, compared to the ompK36 crystal structure, chain A of PDB code 1osm (SEQ ID NO:24). The alpha-carbon CRMS for the best aligning 259 residues (80% of the complete 323 residues) is 3.11 Å.

35) Please delete the paragraph starting on page 46, line 17 with "Figure 37 shows ..." and ending on page 47, line 2 with "...is 2.26 Å." and replace the deleted paragraph with the following replacement paragraph:

Figure 37 shows the alignment, formed from the methods according to the invention, in PIR format, between the sequence of sucrose-specific porin, denoted 1a0tP (SEQ ID NO: 26), and the sequence of maltoporin, chain A of PDB

structure 2mpr, denoted 2mprA (SEQ ID NO: 25). In total, 410 residues are aligned to the template, and the sequence identity is 21%. Figure 38 shows a rainbow ribbon overlay between the three-dimensional structure created using the alignment in figure 37, compared to the sucrose-specific porin crystal structure, chain P of PDB code 1a0tP (SEQ ID NO: 26). The alpha-carbon CRMS for the best aligning 328 residues (80% of the complete 410 residues) is 2.26 Å.